2.0 RESPONSE

2.1 STATUS OF THE CLAIMS

Claims 1-38 were pending at the time of the Restriction Requirement.

Claims 36-38 were previously canceled without prejudice and without disclaimer as being drawn to a non-elected invention.

Claims 1 to 35 were examined on the merits, and claims 32-34 were also withdrawn from consideration as being directed to a non-elected invention. Applicants confirm cancellation of these claims herein without prejudice and without disclaimer.

Claims 1-31 and 35 have been amended herein.

Claims 39 and 40 have been added herein.

Claims 1-31, 35, and 39-40 are now pending in the application. In accordance with 37 C. F. R. § 1.121, the pending claims are listed in the amendment section.

2.2 SUPPORT FOR THE CLAIMS

Support for the revised and newly added claims exists throughout the specification and claims of the original applications as filed. In light of the claims canceled to date, no fees should be required for the two new claims. Applicants certify that no new matter was added as a result of the present amendment.

2.3 THE OBJECTION TO THE OATH/DECLARATION IS OVERCOME.

(Action at page 2, Item 2)

The Action indicates that oath or declaration is considered defective. To that end, Applicants hereby submit a new declaration in compliance with 37 C. F. R. §1.67(a).

Applicants respectfully request that the objection now be withdrawn.

2.4 THE OBJECTION TO THE SPECIFICATION IS ERRONEOUS.

(Action at page 3, Item 3)

The disclosure was objected to allegedly because of informalities with respect to compliance with the sequence listing requirements. Applicants respectfully traverse.

Applicants submitted on October 20, 2003 a response to the request for a sequence listing in compliance with the relevant statutes and regulations. This response included an amendment to the specification to insert the required sequence identifiers throughout the text. Applicants do not find in either the present action, or the Restriction Requirement dated July 29, 2004, that the Office received and/or entered Applicants' previous amendment.

Applicants attach hereto a courtesy copy of that amendment as **Exhibit A**, including the dated postcard evidencing receipt by the Office of those papers, and ask that the Amendment be made of record.

Applicants formally request that the previous amendment be entered and made of record. Applicants believe that doing so places the specification into full conformity with the sequence listing requirements, and asks that the present objection therefore be withdrawn.

2.5 THE OBJECTIONS TO THE CLAIMS ARE OVERCOME.

(Action at page 3, Items 4 & 5)

Claims 1, 11, 16, and 35 have been objected to because the claims recite non-elected compounds of formula I. Claim 30 was objected to allegedly for use of a non-American English spelling of the word "synthesizing". Applicants respectfully traverse.

However, in an effort to progress the case to allowance, and to focus on other substantive issues, Applicants have nevertheless improved the language of the cited claims to overcome the concerns of the Office. Applicants therefore request that the objection be withdrawn.

2.6 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 112, 2ND PARAGRAPH, IS OVERCOME.

Claims 1-29 and 35 were rejected under 35 U. S. C. § 112, 2nd paragraph, allegedly as being indefinite. (Action at pages 3-5, Items 6-15)

Applicants respectfully traverse. However, Applicants appreciate the helpful suggestions of the Examiner to further improve the clarity and to more distinctly point out and claim aspects of the present invention. To that end, claims have been amended to address the particular clarity issues raised by the Office.

Claims 1 and 14 have been clarified with the recitation of "a primary amine nitrogen atom to form a secondary amine," and the general formula II.

Claim 4 has been clarified to recite "a halogenated methyl group."

Claim 7 has been clarified to provide proper antecedent basis to claim 1, which has also been amended to reflect compounds of the general formula II.

With respect to claims 12-15, 24, 25, and 35, Applicants assert that the term "difficult peptide" is not indefinite, and is well known in the peptide synthetic arts. "difficult" sequences are discussed at pages 7 lines 1 to 21, and at page 9 line 32 to page 10 line 1. Cyclic peptides of up to 10 amino acids are recognized in the art as particularly "difficult" (see page 21 lines 7-9). Non-cyclic "difficult" sequences are aldo discussed at page 52, lines 7-16, and page 55, lines 12014.

The Examiner is also invited to examine the references previously of record in Applicants' Information Disclosure Statement for extensive examples of the use of this term in the art:

Hyde *et al, Int. J. Pept. Prot. Res.,* 1994 43:431-440 (particularly column 1, paragraph 1 and references cited therein)

Johnson *et al, J. Pep. Sci.,* 1995, 1:11-25.

Johnson *et al., Tetrahedron Lett.,* 1994, 35:463-466.

Applicants respectfully request that in view of this well-known term of art, the rejection of these claims be withdrawn.

With respect to claim 20, clarity has been achieved by deleting the optional step of "removal of side chain protecting groups."

With respect to claims 17-21 and 23, Applicants note that it would be clear to one of skill in the art that upon a fair reading of the specification as a whole, that any primary amino group and any carboxylic acid group may be targeted, since the method of the invention can be used to effect cycliczation by linking either a C-terminal carboxylic acid or a side-chain carboxylic acid (*i.e.,* aspartate or glutamate). However, in an attempt to provide even greater clarity and definition to the claim, Applicants have offered the term "selected" to replace "desired" in claim 17. Applicants believe this fully addresses the clarity concerns of the Office and request that the rejection be withdrawn.

Claim 22 has been clarified to identify a "C-terminal carboxylic acid" of the second peptide is activated. Applicants believe that it would be clear to one of skill in the art when considering a fair reading of the specification as a whole that the recited "fragments" are portions of the large peptide which is to be synthesized, and that the method is applicable to *any* target

large peptide. It would be evident that other fragments of the target peptide would be linked together in similar fashion, and that any suitable method (such as an enzymic method, for example) could be used to link the larger fragments thus produced to form the ultimate target large peptide. It would be clear to one of skill in the art that one could employ the method in claim 22 to form a peptide bond between two short peptide fragments A and B, then add the auxiliary to this product, and ligate a third fragment C to produce a peptide A-B-C. Applicants submit that the claims are not indefinite, and respectfully request that the clarity rejection be withdrawn.

Claim 26 has been clarified to recite "the α-nitrogen of an amino acid residue in the selected peptide to a solid support." Applicants believe this addresses the clarity issue with respect to the language of claim 26.

Claims 27 and 28 have also been clarified to be consistent with the claims from which they depend, and to more properly define a "C-terminal amino acid residue of the selected peptide is a modified carboxylic acid in which the carboxyl group is replaced by a functional group," and to clarify that the functional group may be selected from the group consisting of an ester, an alkylalcohol, an acetal, or an amide group. Applicants believe that this clarification readily overcomes the issue raised by the Examiner and asks that the rejection now be withdrawn.

The various claims have also been clarified to conform more properly to U.S. format, and to correct the spelling of various terms that have a slightly different non-American English spelling.

New claims 39 and 40 have been added to claim additional aspects of the invention commensurate in subject matter with the elected restriction.

Applicants believe this to be a complete response to the rejections under this section of the Statutes, and respectfully request that all rejections be withdrawn for all pending claims.

2.7 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 102, IS OVERCOME.

Claims 1-3, 6-8 and 14 were rejected under 35 U. S. C. § 102, allegedly as being anticipated by Bodanszky. (Action at page 5-6, Item 16)

Applicants respectfully traverse.

Applicants appreciate the Examiner's understanding of the clear distinction between the method disclosed in Bodanszki and that of the present invention. Applicants also appreciate the helpful suggestion of the Examiner in more clearly distinguishing the claims in the present application in view of the cited reference. Applicants have amended claims 1 and 14 to specify the further steps of forming a secondary amine, and converting the secondary amine to an amide, thereby forming the peptide bond. Passages of the Specification at pages 33, 37, 41, and 42 also provide alternative means for achieving these steps.

As Bodanszki does not teach or fairly suggest each and every limitation of the claims, Applicants respectfully request, therefore, that the rejection be withdrawn.

Claims 1, 3, 6-8 and 14 were rejected under 35 U. S. C. § 102, allegedly as being anticipated by Ehrlich* et al. *(Action at page 6, Item 17)

The Action states that this reference "discloses the same method step of linking an aromatic carbonyl group to an amine nitrogen as the claimed method." Applicants respectfully traverse.

Ehrlich discloses a method for cyclization of three thymopentin-derived penta- and hexapeptides. The best results were obtained with the auxiliary 2-hydroxy-4-methoxybenzene (HmB), which is attached at position 3 from the C-terminus (compound 12, Table2). In contrast to the auxiliary of the present invention, HmB ***does not*** have an electron withdrawing group Y, and there is no teaching or suggestion in Ehrlich that such an electron withdrawing group would confer any advantage.

As described on the right-hand column of page 8834 and the left-hand column of page 8835 of the reference, the addition of HmB within the peptide sequence results in a doubling of yield of cyclic material. The mechanism for this increase in yield is outlined in the last sentence of the abstract, which states that "reversible amide bond alkylation such as HmB-modification should be useful in promoting the cyclisation of peptides devoid of turn-inducing amino acid residues". This is further supported by the statement in the right -and column of page 8835 that "(A)n alternate method of inducing cyclization-prone conformations by N-acylation of the peptide bond via $(Boc)_2O$ was recently reported". The abstract (last sentence) identifies a third method of inducing cyclization, namely N-methylation of the amide bond.

It has been known in the art that alkylation of the amide bond (Me, Boc or HmB) results in an increase in amide bond flexibility and the possibility of populating *cis* conformations, which, to quote Ehrlich et al, "induces cyclization-prone conformations". The HmB group does *not* participate in the cyclization itself; it merely promotes turn conformations which *aid* in the process of cyclization. That is the primary motivation for incorporating HmB towards the middle of the peptide sequence.

In contrast to the disclosure of Ehrlich et al., and as outlined in Scheme 13 of the present Specification, the representative auxiliary of the present invention, HnB, *directly participates* in

the final cyclization reaction. The significant gains in yield of cylic peptides and the ability to prepare cyclic peptides which are considered to be intractable using traditional methods result from the chemical character of the auxiliary of the present invention and its capacity of rapid acyl transfer.

In fact, Elrich *et al.* admits one of the key limitations in the art when using HmB. "Because of hindrance of coupling to a N-substituted amino acid, the next amino acid (Lys) was coupled overnight." (right-hand column of page 8835). It is also important to note that this is with respect to *coupling* an amino acid, not cyclization of a peptide. In fact, the present specification (for example, at page 11, line12) teaches that these very limitations in coupling *can be overcome* by using an auxiliary of the present invention such as HnB.

As previously pointed out, HmB does not have an electron-withdrawing group Y, and there is no teaching or suggestion in Ehrlich *et al.* that such a group would confer any advantage. There is also no teaching or suggestion in Ehrlich *et al.* for using HmB to participate in the final cyclization reaction.

As pointed out in the Specification at page 11 lines 12 to 28, HmB suffers from two major limitations; these limitations are overcome by the auxiliary of the present invention. As stated above, the HmB group as used by Ehrlich is not involved in the cyclization step; in contrast, it is distant from the final cyclization point, and is used only to provide backbone protection. The presence of the HmB group alters the conformation of the peptide from *trans* to *cis*, making a peptide which was previously devoid of turn-inducing amino acid residues more cyclization-prone. However, it does not bring the two ends of the peptide together to facilitate cyclization. In particular, Ehrlich does not disclose or suggest acyl transfer.

Thus, since Ehrlich et al. neither teaches nor fairly suggests the claimed invention, Applicants respectfully request that the rejection be withdrawn.

2.8 THE PROVISIONAL REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING IS NOTED.

Claims 1-21, 23, 30, 31 and 35 were provisionally rejected for obviousness-type double patenting over commonly owned co-pending application 09/806,036. (Action at pages 7-8, Item 18)

Applicants respectfully traverse. However, they note for the record that the cited application and the present application are commonly owned, and as such, the rejection may be overcome by submission of an executed terminal disclaimer in compliance with 37 C. F. R. § 1.321(b)(c) and (d), disclaiming the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U. S. C. §§ 154 to 156 and 173, as shortened by any terminal disclaimer, of a patent that would grant based upon the co-pending application which is commonly owned with the present application.

Applicants also note for the record, however, that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. vs. Union Sanitary District,* 20 USPQ 2d 1392 (Fed. Cir. 1991).

The Court in *Quad* indicated that:

> "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection."

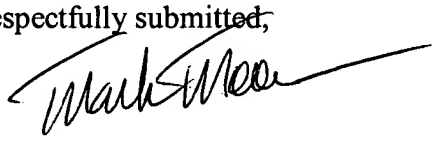
Applicants elect to defer submission of that paper until such time as all claims are allowed in the present case. Applicants therefore request that the Rejection be held in abeyance until a notice of allowability is received.

3.0 CONCLUSION

It is respectfully submitted that all pending claims are fully enabled by the Specification, and that all claims are definite, and free of any concerns of prior art. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in conditions for ready allowance, and that all of the concerns of the Examiner have been resolved. Applicants further respectfully request, therefore, the withdrawal of all rejections and that a Notice of Allowance be issued in the case with all due speed. However, Applicants also note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' new representative would be appreciated.

Respectfully submitted,



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This paper and fee are being deposited with the U.S. Postal Service Express Mail Post Office to Addressee service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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